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A 58-year-old man developed symptoms of hyperthyroidism and congestive heart failure. While hyperthyroid, his serum thyrotropin (TSH) level was inappropriately elevated at 6.1 μU/ml. The molar ratio of alpha subunit to TSH was 2.5, suggesting the presence of a TSH secreting pituitary tumor. Further evaluation disclosed an enlarged sella turcica with posterior erosion, and an intrasellar mass was visualized on CT scan. Neither serum TSH nor alpha subunit levels became elevated after thyrotropin-releasing hormone, nor were they suppressed by a dopamine infusion. Serum TSH but not alpha rose during

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antithyroid drug therapy. Estrogens produced a partial reduction in serum alpha (presumably reflecting the non-tumorous gonadotroph contribution to circulating alpha subunit). Dexamethasone completely suppressed serum TSH but had no effect on alpha, suggesting a differential feedback of glucocorticoids on TSH and alpha secretion. The patient was treated with pituitary irradiation rather than surgery because of his underlying heart disease.

Hyperthyroidism due to a Thyrotropin-Secreting Pituitary Adenoma

Studies of Thyrotropin and Subunit Secretion

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• **A 58-year-old man had symptoms of hyperthyroidism and congestive heart failure. While hyperthyroid, his serum thyrotropin (TSH) level was inappropriately elevated at 6.1 μU/mL. The molar ratio of alpha subunit to TSH was 2.5, suggesting the presence of a TSH-secreting pituitary tumor. Further evaluation disclosed an enlarged sella turcica with posterior erosion, and an intrasellar mass was visualized on computed tomographic scan. Neither serum TSH nor alpha subunit levels became elevated after administration of thyrotropin-releasing hormone, nor were they suppressed by a dopamine infusion. Serum TSH but not alpha subunit levels rose during antithyroid drug therapy. Estrogens produced a partial reduction in serum alpha subunit concentration (presumably reflecting the nontumorous gonadotroph contribution to circulating alpha subunit). Dexamethasone completely suppressed serum TSH level but had no effect on the alpha subunit level, suggesting a differential feedback of glucocorticoids on TSH and alpha secretion. The patient was treated with pituitary irradiation rather than surgery because of his underlying heart disease.**

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Thyrotropin (TSH)-secreting pituitary tumors have become increasingly recognized as a cause of hyperthyroidism.[1-6] Diagnosis requires measurement of inappropriate levels of serum TSH, and may be associated with elevated levels of the alpha subunit of TSH.[3] We recently studied our second patient with this disorder, in whom several diagnostic tests were performed that to the best of our knowledge had not previously been done in such patients. These results provide new information that furthers our understanding of this fascinating disorder.

REPORT OF A CASE

A 58-year-old man had heat intolerance, atrial fibrillation, and congestive heart failure. He had a 50-g thyroid gland, warm skin, a tremor, a pulse rate of 90 beats per minute, neck vein distention, rales, an S_3 gallop, and pretibial edema. Exophthalmos and lid lag were absent, and visual fields were normal. Thyroid studies gave the following values: thyroxine (T_4), 15.5 μg/dL (normal, 5.1 to 10.8 μg/dL); free T_4, 2.8 ng/dL (normal, 0.8 to 2.3 ng/dL); TSH, 6.1 μU/mL (hyperthyroid, < 0.75 μU/mL); TSH-β, 0.5 ng/mL; alpha subunit, 3.9 ng/mL (normal, < 2.0 ng/mL); radioactive iodine uptake, 35% (normal, 8% to 30%), reverse triiodothyronine, 116 ng/dL (normal, < 50 ng/dL); and thyroxine-binding globulin capacity, 13.8 μg/dL (12 to 38 μg/dL). Thyroid antibodies and long-acting thyroid stimulator were undetectable. Roentgenograms were abnormal (Fig 1). Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and prolactin levels were normal. Cortisol and growth hormone concentrations rose normally after insulin-induced hypoglycemia. Tests of peripheral hormone action included an O_2 consumption of 369 mL/min (normal, 240 to 400 mL/min); RBC sodium value, 8.4 mmole/L (normal, 6.2 to 8.2 mmole/L); serum free fatty acid concentration, 762 mEq/L (normal, 340 to 725 mEq/L); carotene level, 42.3 μg/dL (normal, 50 to 300 μg/dL); and urinary creatine excretion, 0.03 to 0.08 g/24 hr. The metabolic clearance and production rates of 3',5'-diiodothyronine were 333 L/day/70 kg and 19.3 μg/day/70 kg, respectively.[7]

Fig 1.—Polytomogram of sella turcica in man with inappropriate thyrotropin secretion and hyperthyroidism shows enlargement and ballooning of sella. (Skull x-ray films also showed enlargement with posterior erosion, and computed tomographic scan demonstrated intrasellar mass with no suprasellar extension.)

The responses of TSH and alpha subunit to a variety of stimuli are detailed in Fig 2. Basal serum TSH concentration was inappropriately elevated in view of high total and free T_4 levels. Thyrotropin-releasing hormone (TRH) stimulation tests (Fig 2, [illegible]t and right and bottom left) showed a basal TSH level of 3.2 [illegible] U/mL and alpha subunit level of 2.3 to 2.7 ng/mL, with no [illegible]o TRH. The TSH-β level was 1.0 ng/mL, and prolactin v[illegible] unresponsive to TRH. The serum TSH level increased from 6.5 to 10.3 μU/mL as T_4 levels were reduced with propylthiouracil. Alpha subunit levels bore no relation to serum T_4 or TSH concentrations, and ranged from 2.8 to 4.7 ng/mL. The serum prolactin value increased from 7.3 to 16.8 ng/mL after TRH during propylthiouracil-induced euthyroidism. Prednisone reduced serum TSH level from 10.2 to 0.8 μU/mL, while alpha subunit and TSH-β concentrations were unchanged (Fig 2, top center). Thyrotropin-releasing hormone produced a small TSH response with no rise in alpha subunit or TSH-β levels. Serum prolactin level rose to 14.4 ng/mL while the patient received prednisone.

To evaluate the contributions of LH-α and FSH-α subunits to total serum alpha subunit concentration,[8] the patient received estrogens to suppress LH and FSH-α. The LH level decreased from 11.0 to 8.0 ImU/mL and the FSH level from 10.8 to 5.9 ImU/mL. The TSH concentration rose slightly, but the alpha

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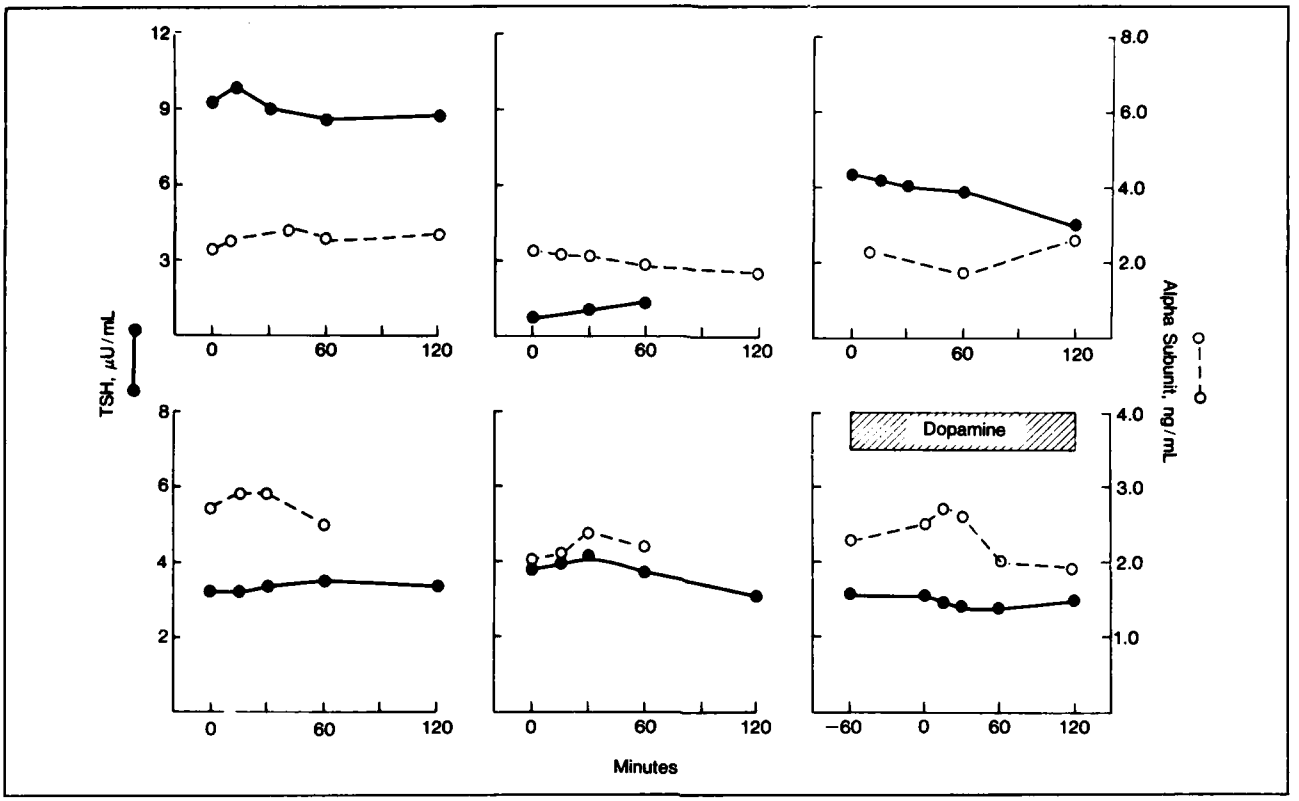

Fig 2.—Serum thyrotropin (TSH) and alpha subunit responses to thyrotropin-releasing hormone (500-μg intravenous bolus at time 0) in man with hyperthyroidism due to TSH-secreting pituitary adenoma. Top left, Hyperthyroid patient immediately before prednisone suppression; top center, after receiving prednisone, 20 mg every eight hours for two days; top right, after cessation of prednisone therapy; bottom left, immediately before estrogen administration; bottom center, while receiving conjugated estrogens, 2.5 mg/day, for four days to suppress luteinizing hormone and follicle-stimulating hormone alpha; bottom right, during three-hour dopamine infusion monitored to keep systolic BP 5 mm Hg above basal value.[9]

subunit value fell from a mean of 2.8 (n = 3) to 2.0 ng/mL. Testing with TRH (Fig 2, bottom center) produced only a slight increase in TSH and alpha subunit levels during estrogen therapy, while TSH-β concentration was unchanged. The patient was also given dopamine while receiving estrogen. A three-hour infusion (Fig 2, bottom right) produced no change in serum TSH concentration, whereas alpha subunit level fell slightly from 2.3 to 1.9 ng/mL; the TSH-β level remained stable at 0.5 ng/mL. Furthermore, TRH failed to stimulate either TSH or alpha secretion. The prolactin level decreased from 8.5 to 5.1 ng/mL after one hour and to 2.3 ng/mL during the second hour of infusion despite the administration of TRH. After completing these evaluations, propylthiouracil therapy was reinstituted and the patient received pituitary irradiation (4,600 rad). One year later, he still required propylthiouracil to remain euthyroid.

COMMENT

Our patient had no stigmata of Graves' disease. His serum TSH level was measurable despite increased serum total and free T_4 levels, and was associated with roentgenographic evidence of a pituitary tumor. Although his serum alpha subunit level was only slightly elevated, the alpha subunit-TSH ratio of 2.5 further supports the diagnosis of a pituitary tumor.[3]

Several tests of dynamic function were performed. The lack of TSH and alpha subunit responses to TRH suggests that the tumor thyrotrophs were autonomous. This test may be useful, as patients with hyperthyroidism due to inappropriate TSH secretion but without evidence of a pituitary tumor usually respond to TRH.[6] The effect of glucocorticoids on these tumors may provide useful information, since secretion of both TSH and alpha subunit is usually suppressed by glucocorticoids. In the present case, prednisone had no effect on alpha, while TSH level was markedly reduced. The failure of prednisone to suppress serum alpha subunit while completely suppressing TSH could indicate differential feedback of glucocorticoids on TSH and alpha secretion. Although alpha subunit is a marker for pituitary tumors, some of the serum alpha measured in these patients may be derived from nontumor cells. Kourides et al[8] demonstrated two different pools of alpha subunits. We found that estrogen administration reduced serum alpha subunit concentrations in our patient by 28%, suggesting either that a portion of this circulating subunit was derived from gonadotrophs or that the tumor response to estrogens differs from that of normal pituitary tissue. Dopamine infusions in normal men suppress serum TSH and blunt the TSH response to TRH.[9] In our study, dopamine had no suppressive effect on TSH whereas prolactin concentration was reduced, suggesting the presence of an altered receptor for dopamine on the tumor thyrotrophs.

Our patient demonstrated that many of the usual mechanisms regulating TSH secretion are deranged in a thyrotropic tumor. These included abnormal TSH and/or alpha subunit responses to thyroxine, TRH, glucocorticoids, and dopamine. Moreover, our estrogen study implies that interpretation of alpha subunit values in such patients should take into account the contribution of nonthyrotroph cells to the circulating subunit pool. Although all TSH-secreting tumors to date have been large and readily recognized

roentgenographically, it is possible that microadenomas may be identified in the future by the types of dynamic studies described herein.

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Bruce Weintraub, MD, measured serum alpha subunit and TSH-β levels. Nancy Whorton provided technical assistance in measuring TSH levels.

A complete list of references is available on request of the authors.

References

1. Jailer SW, Holub DA: Remission of Graves' disease following radiotherapy of a pituitary neoplasm. *Am J Med* 1960;28:497-500.

2. Faglia G, Ferrari C, Neri V, et al: High plasma thyrotropin levels in two patients with pituitary tumors. *Acta Endocrinol* 1972;69:649-658.

3. Kourides IA, Ridgway EC, Weintraub BD, et al: Thyrotropin-induced hyperthyroidism: Use of alpha and beta subunit levels to identify patients with pituitary tumors. *J Clin Endocrinol Metab* 1977;45:534-543.

4. Smallridge RC, Wartofsky L, Diamond RC: Inappropriate secretion of thyrotropin: Discordance between the suppressive effects of corticosteroids and thyroid hormone. *J Clin Endocrinol Metab* 1979;48:700-705.

5. Waldhausl W, Bratusch-Marrain P, Nowotny P, et al: Secondary hyperthyroidism due to thyrotropin hypersecretion: Study of pituitary tumor morphology and thyrotropin chemistry and release. *J Clin Endocrinol Metab* 1979;49:879-887.

6. Weintraub BD, Gershengorn MC, Kourides IA, et al: Inappropriate secretion of thyroid-stimulating hormone. *Ann Intern Med* 1981;95:339-351.

7. Smallridge RC, Burman KD, Smith CE, et al: Metabolic clearance and production rates of 3',5'-diiodothyronine in hyperthyroidism and hypothyroidism in man: Comparison of infusions using radiolabeled versus unlabeled iodothyronine. *J Clin Endocrinol Metab* 1981;52:722-730.

8. Kourides IA, Weintraub BD, Re RN, et al: Thyroid hormone, estrogen, and glucocorticoid effects on two different pituitary glycoprotein hormone alpha-subunit pools. *Clin Endocrinol* 1978;9:535-542.

9. Besses GS, Burrow GN, Spaulding SW, et al: Dopamine infusion acutely inhibits the TSH and prolactin responses to TRH. *J Clin Endocrinol Metab* 1975;41:985-988.

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